MS05-O2

From fragments to in vivo activity using X-ray crystallography: the discovery of potent inhibitors of the KEAP1-NRF2 protein-protein interaction

Tom Davies[1]

1. Astex Pharmaceuticals, Cambridge, United Kingdom

email: tom.davies@astx.com

KEAP1 is the key regulator of the NRF2-mediated cyto-protective response, and an attractive target for diseases involving excessive oxidative stress. Direct antagonism of the KEAP1-NRF2 protein-protein interaction presents a novel opportunity for pharmacological intervention, but identifying inhibitors with drug-like properties has been challenging. In collaboration with GSK, we have applied our fragment-based approach (PyramidÔ) to develop KI-696, a small-molecule KEAP1-NRF2 antagonist which combines high potency with physicochemical properties suitable for biological evaluation. X-ray crystallographic screening led to the identification of fragments bound at multiple "hot-spots" within the KEAP1 Kelch domain, and this information was used to elaborate a weakly binding hit (K_d>1 mM) to a potent lead (K_d1.3 nM). KI-696 exhibits good selectivity for KEAP1, and activates the NRF2 antioxidant response in cellular and *in vivo* models, thereby providing a high quality chemical probe to explore the therapeutic potential of disrupting the KEAP1-NRF2 interaction.

MS05-O3

Effective crystal structures in pharmaceutical development

Sophie Janbon[1]

1. AstraZeneca, Pharmaceutical Science, Macclesfield, United Kingdom

email: sophie.janbon@astrazeneca.com

Most crystalline compounds exhibit polymorphism.[1] This is the ability of a chemical substance to pack in different 3-D arrangements. Different polymorphs usually mean different physical and chemical properties. As a result, the pharmaceutical industry invests a significant amount of resources and capabilities in a wide range of polymorph risk-assessment tools [2] to avoid the appearance of a more stable crystalline form of the Active Pharmaceutical Ingredient (API) late in drug development or after launch. One of the main risk of not identifying the most stable form early in drug development is that the business may not guarantee the supply of medicine to patients on time for clinical phases as well as post-launch. Example [3] has existed and showed the criticality of understanding the solid form landscape of any new chemical entity. In the armoury of polymorph risk assessments, the assessment of crystal structure data has become invaluable and this is the main topic of this presentation. This is now a core activity within AstraZeneca, performed on all suitable API's in the portfolio, to 1) guide our experiments, 2) enhance our understanding and 3) risk assess the likelihood of identifying a more stable form. The implementation of the crystal structure assessments has also become an integral part of our form selection process. Following the selection of the solid form for the development and/or commercial phases, crystal structures continue to guide decision-making during the development of commercial processes and control strategies for registered starting materials, chemical intermediates, API's and formulated medicines. Examples of how crystal structures are assessed via a step-wise method, used in our business will be presented using AZ compounds.

References:

[1] Mullin, J. W. (2001). Crystallization (4th. ed.). Oxford: Reed Educational and Professional Publishing Ltd.

[2] Lee, E-H. (2014). A practical guide to pharmaceutical polymorph screening & selection. Asian Journal of Pharmaceutical Sciences, vol. 9, pp. 163-175.

[3] Chemburkar, S.R.; Bauer, J.; Deming, K.; Spiwek, H.; Patel, K.; Morris, J.; Henry, R.; Spanton, S.; Dziki, W.; Porter, W.; Quick, J.; Bauer, P.; Donaubauer, J.; Narayanan, B.A.; Soldani, M.; Riley, D. and McFarland, K. (2000). Dealing with the Impact of Ritonavir Polymorphs on the Late Stages of Bulk Drug Process Development. Organic Process Research & Development, vol. 4, pp. 413-417.

Keywords: Crystal structures, Polymorphs, Risk assessments